Bayer

Pharmaceutical Division

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

5711 '99 APR 14 A

April 13, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Sir/Madam:

Enclosed are our comments on the "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System" draft guidance which was published at http://www.fda.gov/cder/guidances/index.htm.

Sincerely,

Chetan D. Lathia

Chetan D. Lathia, PhD
Associate Director,
Clinical Pharmacology

Cc:

Carl Calcagni
David Goldman
Allen Heller
Alan Hollister
John Lettieri
Arthur Mazzu
Pavur Sundaresan
Anita Shah
Paul Mac Carthy

99D-0121

C 2

This document published by the FDA provides guidance on when it is appropriate to request waiver for conducting in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms. Overall, it is a very well written and scientifically sound document. We feel that this guidance will allow the pharmaceutical industry to request waivers for unnecessary bioequivalence and bioavailability studies when it is scientifically appropriate. There are some practical aspects in the document relating to methodologies that need to be clarified, critically discussed and/or reconsidered. We offer the following comments, with text from the proposed draft guidance in quotations in some instances, for the sections indicated below:

Section II. Background

It may be worthwhile to state that the proposed guidance applies to prescription drugs and not to Over The Counter (OTC) medications.

Section III B. Permeability

"A drug substance is considered highly permeable when the extent of absorption in humans is determined to be >90% of an administered dose based on a mass-balance determination, or in comparison to an intravenous reference dose in the absence of evidence suggesting instability in the gastrointestinal tract."

We interpret this section as the FDA requiring information on the extent of absorption in man to classify a drug as having high permeability. We think that, with certain exceptions, it is very difficult to evaluate the extent of absorption in man. In a mass-balance study, if a drug is given orally, it is usually impossible to distinguish between the amount excreted in feces and the amount that is unabsorbed. We also think that it may not be possible to evaluate absorption using an intravenous dosage form as a reference because of 3 potential reasons: a) It is not possible to formulate an intravenous dosage form b) It is not appropriate to administer the intravenous dosage form due to toxicity concerns c) It is not possible to quantitate parent and all metabolites for unlabeled drug given orally and intravenously. Therefore, we suggest that this requirement be seriously reconsidered. We interpret information presented in Section IV B. 2 as contradictory to the information presented in Section III B. This should be clarified in the final guidance.

Section IV B. Determining Permeability Class

"To be classified as highly permeable, a test drug should have an extent of absorption > 90% in humans".

As stated earlier, we think that it is usually very difficult to establish the extent of absorption in man.

Section IV B. 1. Studies of the Extent of Absorption in Humans

"For mass-balance studies using a radiolabeled drug, serial blood, urine, and fecal samples should be collected for about 10 elimination half-lives."

We feel that for a drug with an elimination half-life over 48 hours it becomes logistically very difficult to collect blood, urine, and fecal samples for 10 elimination half-lives. For example, if the half-life were 3 days, this would mean keeping the subjects in-house for 30 days (10 half-lives) to get reliable and complete collections of excreta. We feel that this is a very stringent requirement. Instead, we feel that excreta should be collected to obtain 90% recovery.

Section IV B. 2 Intestinal Permeability Methods

"The following methods can be used to determine the permeability of a drug from the gastro-intestinal tract:"

While it appears that one of the four methods is recommended to evaluate permeability, it is not clearly stated in the document. We suggest that this be clearly stated.

"A correlation can be established using 20 or more selected drugs for which reliable estimates of extent-of-absorption and information on absorption mechanisms (including potential for intestinal efflux via p-glycoprotein or other efflux systems) are available. When a method enables the selected model drugs to be categorized into the correct permeability class, that method can be considered useful for the BCS and can be used to determine the permeability class membership of test drugs."

We think that this is an excellent way of determining permeability. However, we feel that the statement above is contradictory to statements made earlier in Sections III B and IV B about requiring data for extent of absorption in man. We interpret this paragraph and the one that follows as allowing an in vitro/in situ method to establish permeability after establishing a correlation between in vitro/in situ methods used by the sponsor applying for biowaiver and the extent of absorption data for 20 or more selected drugs. Please provide a reference for these data or provide these data in an appendix to the document. We agree with this approach and strongly recommend that the agency adopt it, if that is not the case now. If the intent of the agency is to use the approach stated above as opposed to determining the extent of absorption in man, this must be clarified in the final guidance.

Section V. 6. All other application commitments should be met.

Please clarify or provide a reference on the details of 'other application commitments'.

Section VI A. Instability in the Gastrointestinal Tract

"Drug solutions in these fluids can be incubated at 37°C for about three hours and analyzed using a validated stability indicating assay. Significant degradation or loss (>5%) of a drug in about three hours could suggest potential instability."

Please clarify what does a 'validated stability indicating assay' means and provide a reference for this. Additionally, you propose evaluating a 5% loss of drug. In our experience, assays used to determine drug concentrations in biological fluids generally have a 10% coefficient of variation in their quality controls. It is very difficult to determine a loss of 5% when the acceptable coefficient of variation for QCs is 10%.

fedEx. USA Airbill

FedEx Tracking Number 809804743741

Form I.D. No. 0210

Recipient's Copy

1 From

Date 04/13/99

Sender's Name Chetan Lathia PhD Phone (203)812 2768

Company BAYER CORP/PHARM DIVISION

Address 400 MORGAN LN

Dept./Floor/Suite/Room

City WEST HAVEN State CT ZIP 06516

2 Your Internal Billing Reference Information

3 To

Recipient's Name Dockets Management Branch (HFA-305) Phone ( )

Company Food and Drug Administration

Address 5630 Fishers Lane, Room 1061

(To "HOLD" at FedEx location, print FedEx address here)

Dept./Floor/Suite/Room

☐ Check here if residence (Extra charge applies for FedEx Express Saver)

City Rockville State MD ZIP 20852

For HOLD at FedEx Location check here

☐ **Hold Weekday** (Not available with FedEx First Overnight)

☐ **Hold Saturday** (Not available at all locations) (Available for FedEx Priority Overnight and FedEx 2Day only)

For WEEKEND Delivery check here (Extra Charge. Not available at all locations)

☐ **Saturday Delivery** (Available for FedEx Priority Overnight and FedEx 2Day only)

☐ **NEW Sunday Delivery** (Available for FedEx Priority Overnight only)

8 0 9 8 0 4 7 4 3 7 4 1

4a Express Package Service *Packages under 150 lbs.* Delivery commitment may be later in some areas.

XXX FedEx Priority Overnight (Next business morning)

☐ FedEx Standard Overnight (Next business afternoon)

☐ FedEx First Overnight (Earliest next business morning delivery to select locations) (Higher rates apply)

☐ FedEx 2Day (Second business day)

☐ FedEx Express Saver (Third business day)

FedEx Letter Rate not available. Minimum charge: One pound rate.

4b Express Freight Service *Packages over 150 lbs.* Delivery commitment may be later in some areas.

☐ FedEx Overnight Freight (Next business day)

☐ FedEx 2Day Freight (Second business day)

☐ FedEx Express Saver Freight (Up to 3 business days)

(Call for delivery schedule. See back for detailed descriptions of freight services.)

5 Packaging

☐ FedEx Letter XXX

☐ FedEx Pak

☐ FedEx Box

☐ FedEx Tube

☐ Other Pkg.

Declared value limit $500

6 Special Handling (One box must be checked)

Does this shipment contain dangerous goods?*

☐ No ☐ Yes (As per attached Shipper's Declaration) ☐ Yes (Shipper's Declaration not required)

☐ Dry Ice Dry Ice, 9, UN 1845 _____ x _____ kg

☐ Cargo Aircraft Only

*Dangerous Goods cannot be shipped in FedEx packaging.

7 Payment

☐ Obtain Recipient FedEx Account No.

Bill to: XX Sender (Account No. in Section 1 will be billed) ☐ Recipient ☐ Third Party ☐ Credit Card ☐ Cash/Check

(Enter FedEx Account No. or Credit Card No. below)

Total Packages	Total Weight	Total Declared Value*	Total Charges
		$ .00	$

* When declaring a value higher than $100 per shipment, you pay an additional charge. See **SERVICE CONDITIONS, DECLARED VALUE, AND LIMIT OF LIABILITY** section for further information.

Credit Card Auth.

8 Release Signature

Your signature authorizes Federal Express to deliver this shipment without obtaining a signature and agrees to indemnify and hold harmless Federal Express from any resulting claims.

Questions?
Call 1·800·Go·FedEx® (800)463-3339

321

WCSL 1098
Rev. Date 7/98
Part #153023PS
©1994-98 FedEx
PRINTED IN U.S.A.

00763609G5